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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,696	12/05/2003	James A. Williams	D-2939CIPCONDIV1	8640

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 10/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/728,696	WILLIAMS, JAMES A.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/10/05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-37* is/are pending in the application.

4a) Of the above claim(s) *27 and portions of claims 26 and 33* is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,26 and 28-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/13/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

SOJ

DETAILED ACTION

Claims 1-24 and 38 have been canceled.

Amended Claims 25-37 have been submitted.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

1. The information disclosure statement filed June 13, 2005 has been considered.

Election/Restrictions

2. Newly amended claims 26, 27 and 33 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: All previously examined claims comprised SEQ ID No 23 (serotype A), and newly amended claims 26, 27 and 33 either recite serotypes A-G or recite SEQ ID Nos 28, 40, 60, 66 50, 71 and 77 which structurally are independent and distinct species of invention not previously examined.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, portions of claims 26, 33 directed serotypes B-G, and all of claim 27 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Rejections and Objections Maintained

2. ***Double Patenting (Maintained)***The rejection of claims 25-26, 29-33, and 35-37 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 5 of U.S. Patent No. 5,919,665 is traversed on the grounds that the claim

amendments have obviated this rejection and if the rejection has not been overcome, will consider filing a Terminal Disclaimer upon the indication of allowable subject matter.

3. It is the position of the examiner that the rejection had not been obviated because an effective Terminal Disclaimer has not been received therefore the rejection is maintained.. Although the conflicting claims are not identical, they are not patentably distinct from each other because the allowed claims are directed to a species of invention of the instantly claimed genus of botulinum toxins; the allowed species anticipates the instantly claimed genus of botulinum toxins.

4. ***Provisional Obviousness type Double Patenting (Maintained)*** Claims 25-26,32-33 of this application conflict with claims 25, 29, 32, 34, 38 and 41of Application No. 10/271,012. 37 CFR 1.78(b) is traversed on the grounds that the claim amendments have obviated this rejection and if the rejection has not been overcome, will consider filing a Terminal Disclaimer upon the indication of allowable subject matter.

5. It is the position of the examiner that the rejection had not been obviated because an effective Terminal Disclaimer has not been received therefore the rejection is maintained.. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending claims are directed to a species of invention of the instantly claimed genus of botulinum toxins; the copending species anticipates the instantly claimed genus of botulinum toxins that comprise a non-toxin protein sequence.

6. ***Provisional Obviousness type*** **Double Patenting (Maintained)** Claims 25, 29 and 30 of this application conflict with claims 39-41 and 43of Application No. 10/729,122. 37 CFR 1.78(b) is traversed on the grounds that the claim amendments have obviated this rejection and if the rejection has not been overcome, will consider filing a Terminal Disclaimer upon the indication of allowable subject matter.

7. It is the position of the examiner that the rejection had not been obviated because an effective Terminal Disclaimer has not been received therefore the rejection is maintained.. Although the conflicting claims are not identical, they are not patentably distinct from each other because the co-pending claims are directed to a species of invention of the instantly claimed

genus of botulinum toxins; the copending species anticipates the instantly claimed genus of botulinum toxins that comprise a non-toxin protein sequence.

8. ***Provisional Obviousness type*** **Double Patenting (Maintained)** Claims 25-26, 28-29,31,33-35 and 37 of this application conflict with claims 39-41 and 44 of Application No. 10/729,527. 37 CFR 1.78(b) is traversed on the grounds that the claim amendments have obviated this rejection and if the rejection has not been overcome, will consider filing a Terminal Disclaimer upon the indication of allowable subject matter.

9. It is the position of the examiner that the rejection had not been obviated because an effective Terminal Disclaimer has not been received therefore the rejection is maintained.. Although the conflicting claims are not identical, they are not patentably distinct from each other because the co-pending claims are directed to a species of invention of the instantly claimed genus of botulinum toxins; the copending species anticipates the instantly claimed genus of botulinum toxins that comprise a non-toxin protein sequence.

10. ***Claim Objections (Withdrawn)*** Claims 28, and 34 are objected to because of the following informalities for reciting the phrase "wherein the toxin is in a solution has been obviated through amending the claims to recite a different combination of claim limitations.

1. **(Rejection Maintained)** The rejection of claims 25-26,31-33, 35-37 under 35 U.S.C. 102(e) as being anticipated by Dolly et al (US Pat. 6,203,794, effective filling date May 31, 1994) as evidenced by Ledoux et al (1994) is traversed on the grounds that Dolly et al does not specifically disclose, teach or suggest the present invention directed to a soluble recombinant botulinum toxin that comprises a non-toxin protein sequence and a receptor binding domain amino acid sequence of a botulinum toxin.

2. It is the position of the examiner that amended claim 25 is directed to a soluble botulinum toxin, the toxin comprising at least 2 amino acids ("an amino acid sequence") held in

common with the receptor binding domain of a botulinum toxin A neurotoxin, the amino acid sequence of the receptor binding domain need not evidence receptor binding activity, as what is held in common need only be "an amino acid sequence" of this domain.

1. The recitation of the phrase "comprising an amino acid sequence of a receptor binding domain" is being read to include an amino acid sequence being *held in common* with the toxin and the receptor binding domain, and does not require the presence of an additional amino acid sequence, but the recombinant botulinum toxin must comprise an amino acid sequence that is also present in the receptor binding domain of botulinum toxin A. The light chain of botulinum toxin A at positions 408 and 409, comprise an amino acid sequence of the receptor binding domain, specifically the sequence "NN", which is also present at positions 958-959, 969-970, 1020-1021, 1024-1025, 1050-1051, 1125-1126, 1175-1176, and 1241-1242 of the receptor binding domain of botulinum toxin A (see Swiss Prot Accession Number P10845 for the amino acids sequence positions referenced above).

Dolly et al does disclose the instant claimed invention directed to a recombinant botulinum neurotoxin (see Dolly et al, col. 2, lines 25-36), wherein the botulinum toxin is botulinum toxin A, (see Dolly et al, col. 7, lines 18-30; col. 41, claims 2-3). The recombinant botulinum toxin comprises a botulinum toxin light chain portion (see Dolly et al, col. 8, line 2; see Dolly et al, claims 1-3; col. 24, lines 62-65; Example 15), a heavy chain targeting portion and an internalizable portion (see Dolly et al, claim 4, and col. 5, lines 12-14) which are equivalent portions to the C-terminal and N-terminal functions of a botulinum heavy chain. The botulinum toxin is claimed as a pharmaceutical composition (see Dolly et al claim 4) and is in solution with a pharmaceutically acceptable excipient (see Dolly et al, col. 41, lines 66-67). The recombinant botulinum toxin is expressed using a maltose binding protein (see col. 17, lines 29-39) expression vector (see Dolly et al, for example: col. 3, lines 54-66) and would therefore evidence a specific solubility conferred by the expression vector fusion protein. The C-terminal and N-

terminal portions of the heavy chain are bonded one to the other (see Figure 1B) . The light chain and N-terminal of the heavy chain are bonded to each other (see figure 1B). No distinguishing characteristics have been set forth in the claims to show that the claimed product by process "recombinant" limitation would not be the same or equivalent heavy chain obtained by a different process, specifically purified from natural sources. The botulinum toxin is disclosed to be mutated through the addition of a non-toxin sequence, specifically a "cysteine" at the N-terminal of the light chain (see Dolly et al, col. 12, lines 55-61).

An additional embodiment disclosed is the expression of the recombinant light chain as a fusion protein that comprises "a non-toxin protein sequence" that is cleavable by Factor Xa (see Dolly et al col. 28, lines 59-64; figure 1A) or is a GST fusion protein (see Dolly et al, Example 21, col. 31).

3. Dolly et al still anticipates the instantly claimed invention as now claimed, in light of the evidence Ledoux et al provides that defines botulinum toxins to be water soluble proteins (see abstract, page 1095).

4. Applicant asserts that compositions of Dolly et al comprise a recombinant light chain and uses MBP in the formation of the botulinum toxin and the present claims are directed to composition that comprise the C-terminal portion of a heavy chain of botulinum toxin.

5. It is the position of the examiner that Dolly et al's compositions comprise the C-terminal portion of a heavy chain (see Dolly et al col. 7, lines 32-35, that comprise the C-terminal fragment,(heavy chain targeting portion, Dolly et al, claim 4, and col. 5, lines 12-14) of botulinum toxin (see Dolly et al, col. 7, lines 18-30, and col. 41, claims 2-3). Applicant's compositions do not exclude the presence of additional botulinum

neurotoxin chains and therefore still read on the compositions disclosed in Dolly et al for reasons of record and responses set forth above.

New Grounds of Objection Necessitated by Amendment

Specification

8. The amendment filed May 3, 2005 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The changes in amino acid sequence for SEQ ID NO 24 and 32 through the addition of two amino acids to each sequence at the C-terminal, "Met Ala", introduces New Matter into the instant Specification as no original descriptive support could be found for the newly amended sequences. Applicant has not pointed out wherein the instant Specification support for theses changes can be found. Sequences cannot be changed unless specific support forth the sequence changes can be found in the Specification. Applicant is required to cancel the new matter in the reply to this Office Action.

6. Amended Claims 28- 30, 34-36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dolly et al as applied to claims 25-29, and 31 above in view of Williams et al (US Pat. 5,601,823, reference of record, Applicant's USPTO-1449).

1. See discussion of Dolly et al above. Dolly et al teach recombinant botulinum neurotoxin proteins that comprise the heavy chain C-terminal fragment that is capable of being expressed in an aerobic bacteria and is produced as a single polypeptide chain, wherein the single polypeptide chain comprises an additional maltose binding protein polypeptide sequence

coupled to the botulinum toxin but differs from the instantly claimed invention by failing to show the additional coupled polypeptide to be a polyhistidine tract .

2. Williams et al teaches the production of recombinantly produced clostridium (botulinum and difficile(see col. 3, lines 25-29)) toxins as single chain polypeptides (see col. 8, lines 13-22, lines 59-63) either through coupling the toxin to a maltose binding protein polypeptide or to a polyhistidine tract polypeptide (see col. 35, lines 26-49, Example 11) in an analogous art for the purpose of producing large quantities of recombinant toxins for formulation of vaccines and generation of neutralizing antibodies induced to the recombinant clostridium toxins.

3. It would have been obvious to the person of ordinary skill at the time the invention was made to modify the recombinant polypeptide of Dolly et al that comprised a maltose binding protein non-toxin protein with the polyhistidine tract of Williams et al because Williams et al teaches and shows the successful production of recombinant clostridium toxins and teaches prokaryotic expression systems for the attainment of recombinant Clostridial toxins through expression of single polypeptide chains, wherein the single polypeptide chains will bind to a ligand containing column to aid in protein isolation and purification, the polypeptides including either a maltose binding protein or a polyhistidine tract polypeptide tag (pET16b) (see Example 11, column 35), and these methods serve to define means for attainment of high levels of recombinant toxin.

4. The person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining a botulinum C-terminal portion recombinant protein that comprises a polyhistidine tract utilizing the expression system of Williams et al because both Dolly et al and Williams teach the utilization of maltose binding protein expression system for

the recombinant expression of Clostridial toxins and Williams also successfully showed the recombinant expression of a Clostridial toxin using a polyhistidine tract polypeptide which provides the advantage of attaching the polypeptide polyhistidine tract either at the C-terminal end (pET23a-c) or the N-terminal end (pET16b) (see Example 11, col. 35, lines 26-49) of the Clostridial polypeptide depending on the preferred location of the non-toxin polyhistidine tract polypeptide. In the absence of a showing of unexpected results, Dolly et al in view of Williams et al obviate the instantly claimed invention.

Conclusion

2. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
August 31, 2005

L. R. F. Smith

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